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# **Adult Severe Asthma Registries: A Global and Growing Inventory**

Breda Cushen<sup>1,\*</sup>, Mariko Siyue Koh<sup>2,\*</sup>, Trung N Tran<sup>3</sup>, Neil Martin<sup>3,4</sup>, Ruth Murray<sup>5</sup>, Thendral Uthaman<sup>6</sup>, Celine Yun Yi Goh <sup>5,6</sup>, Rebecca Vella <sup>7</sup>, Neva Eleangovan<sup>5,6</sup>, Lakmini Bulathsinhala<sup>5,6</sup>, Jorge F Maspero<sup>8,9</sup>, Matthew J Peters<sup>10</sup>, Florence Schleich<sup>11</sup>, Paulo Pitrez<sup>12</sup>, George Christoff <sup>13</sup>, Mohsen Sadatsafavi <sup>14</sup>, Carlos A Torres-Duque <sup>15,16</sup>, Celeste Porsbjerg<sup>17</sup>, Alan Altraja<sup>18</sup>, Lauri Lehtimäki <sup>19</sup>, Arnaud Bourdin <sup>20</sup>, Christian Taube<sup>21</sup>, Nikolaos G Papadopoulos <sup>22,23</sup>, Csoma Zsuzsanna<sup>24</sup>, Unnur Björnsdóttir<sup>25</sup>, Sundeep Salvi<sup>26</sup>, Enrico Heffler<sup>27</sup>, Takashi Iwanaga <sup>28</sup>, Mona al-Ahmad <sup>29</sup>, Désirée Larenas-Linnemann <sup>30</sup>, Job FM van Boven <sup>31</sup>, Bernt Bøgvald Aarli<sup>32,33</sup>, Piotr Kuna<sup>34</sup>, Cláudia Chaves Loureiro<sup>35,36</sup>, Riyadh Al-lehebi <sup>37</sup>, Jae Ha Lee <sup>38</sup>, Nuria Marina<sup>39</sup>, Leif Bjermer <sup>40</sup>, Chau-Chyun Sheu <sup>41,42</sup>, Bassam Mahboub <sup>43</sup>, John Busby<sup>44</sup>, Andrew Menzies-Gow<sup>45</sup>, Eileen Wang<sup>46</sup>, David B Price <sup>5,6,47</sup> On behalf of ISAR Inventory Study Group

1 Department of Respiratory Medicine, Beaumont Hospital, Dublin, Ireland;

2 Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore, Singapore;

3 AstraZeneca, Gaithersburg, MD, USA;

4 Department of Respiratory Medicine, University of Leicester, Leicester, UK;

5 Optimum Patient Care Global, Cambridge, UK;

6 Observational Pragmatic Research Institute, Singapore, Singapore;

7 Optimum Patient Care, Brisbane, Queensland, Australia;

8 Clinical Research for Allergy and Respiratory Medicine, CIDEA Foundation, Buenos Aires, Argentina;

9 University Career of Specialists in Allergy and Clinical Immunology at the Buenos Aires University School of Medicine, Buenos Aires, Argentina;

10 Department of Thoracic Medicine, Concord Hospital, Sydney, Australia;

11 CHU Sart-Tilman, GIGA I3, University of Liege, Liège, Wallonia, Belgium;

12 Pulmonology Division, Hospital Santa Casa de Porto Alegre, Porto Alegre, Brazil;

13 Faculty of Public Health, Medical University, Sofia, Bulgaria;

14 Respiratory Evaluation Sciences Program, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, Canada;

15 CINEUMO, Respiratory Research Center, Fundación Neumológica Colombiana, Bogotá, Colombia;

- 16 Universidad de La Sabana, Chia, Colombia;
- 17 Department of Respiratory Medicine and Infectious Diseases, Research Unit, Bispebjerg Hospital, Copenhagen, Denmark;
- 18 Department of Pulmonology, University of Tartu and Lung Clinic, Tartu University Hospital, Tartu, Estonia;
- 19 Allergy Centre, Tampere University Hospital, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;
- 20 PhyMedExp, Univ Montpellier, CNRS, INSERM, CHU Montpellier, Montpellier, France;
- 21 Department of Pulmonary Medicine, University Medical Center Essen-Ruhrlandklinik, Essen, Germany;
- 22 Division of Infection, Immunity & Respiratory Medicine, University of Manchester, Manchester, UK;
- 23 Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece;
- 24 Asthma Outpatient Clinic, National Koranyi Institute for Pulmonology, Budapest, Hungary;
- 25 Department of Allergy and Respiratory Medicine, University Hospital, Reykjavik, Iceland;
- 26 Pulmocare Research and Education Foundation, Pune, India;
- 27 Personalized Medicine, Asthma and Allergy, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy;
- 28 Kindai University Hospital, Osakasayama, Japan;
- 29 Microbiology Department, College of Medicine, Kuwait University, Kuwait, Al-Rashed Allergy Center, Ministry of Health, Kuwait City, Kuwait;
- 30 Centro de Excelencia en Asma y Alergia, Hospital Médica Sur, Ciudad de México, Mexico;
- 31 University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD (GRIAC), Department of Clinical Pharmacy & Pharmacology, Groningen, the Netherlands;
- 32 Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway;
- 33 Department of Clinical Science, University of Bergen, Bergen, Norway;
- 34 Division of Internal Medicine Asthma and Allergy, Medical University of Lodz, Lodz, Poland;

35 Pneumology Unit, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal;

36 Centre of Pneumology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal;

37 Department of Pulmonology, King Fahad Medical City, Riyadh, Saudi Arabia, Alfaisal University, Riyadh, Saudi Arabia;

38 Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea;

39 Pneumology Service, Biocruces, Cruces University Hospital, Barakaldo, Spain;

40 Respiratory Medicine and Allergology, Department of Clinical Sciences, Skåne University Hospital, Lund University, Lund, Sweden;

41 Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan;

42 Department of Internal Medicine, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan;

43 Rashid Hospital, Dubai Health Authority (DHA), Dubai, United Arab Emirates;

44 Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, Northern Ireland, UK;

45 Lung Division, Royal Brompton & Harefield Hospital, London, UK;

46 Division of Allergy and Clinical Immunology, Department of Medicine, National Jewish Health and University of Colorado School of Medicine, Denver and Aurora, CO, USA;

47 Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland, UK

**\*These authors contributed equally to this work**

### **Correspondence:**

David B Price, Observational and Pragmatic Research Institute (OPRI) Pte Ltd, 22 Sin Ming Lane, #06-76, Midview City, 573969, Singapore, Tel +65 3105 1489, Email [dprice@opri.sg](mailto:dprice@opri.sg)

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**Aim:**

The International Severe Asthma Registry (ISAR; <http://isaregistries.org/>) uses standardised variables to enable multi-country and adequately powered research in severe asthma. This study aims to look at the data countries within ISAR and non-ISAR countries reported collecting that enable global research that support individual country interests.

**Methods:**

Registries were identified by online searches and approaching severe asthma experts. Participating registries provided data collection specifications or confirmed variables collected. Core variables (results from ISAR's Delphi study), steroid-related comorbidity variables, biologic safety variables (serious infection, anaphylaxis, and cancer), COVID-19 variables and additional variables (not belonging to the aforementioned categories) that registries reported collecting were summarised.

**Results:**

Of the 37 registries identified, 26 were ISAR affiliates and 11 non-ISAR affiliates. Twenty-five ISAR-registries and 4 non-ISAR registries reported collecting >90% of the 65 core variables. Twenty-three registries reported collecting all optional steroid-related comorbidity variables. Twenty-nine registries reported collecting all optional safety variables. Ten registries reported collecting COVID-19 variables. Twenty-four registries reported collecting additional variables including data from asthma questionnaires (10 Asthma Control Questionnaire, 20 Asthma Control Test, 11 Asthma Quality of Life Questionnaire, and 4 EuroQol 5-dimension 5-level Questionnaire). Eight registries are linked to databases such as electronic medical records and national claims or disease databases.

**Conclusion:**

Standardised data collection has enabled individual severe asthma registries to collect unified data and increase statistical power for severe asthma research irrespective of ISAR affiliations.

## Introduction

Severe asthma is defined as uncontrolled asthma despite adherence to optimised controller therapy and treatment of contributory factors, or that worsens when high-dose treatment is decreased.<sup>1</sup> Although severe asthma is relatively rare, it deserves particular attention because it accounts for a substantial proportion of total asthma morbidity, mortality, and cost. For example, patients with severe asthma experience high exacerbation and hospitalisation rates, limitation of health-related quality of life, and high oral corticosteroid (OCS) burden.<sup>2–5</sup> The increased cumulative incidence in all-cause adverse outcomes from OCS initiation has shown associations with greater healthcare resource utilisation and costs.<sup>6</sup> A 2021 study in Spain estimated an individual cost of €758.70/exacerbation<sup>7</sup> per patient, whereas a 2018 study in France estimated a mean annual asthma-related cost of €8222/year per patient.<sup>8</sup> Moreover, a 2019 study from the US reported costs of patients receiving steps 4 and 5 of the GINA therapy of USD15,244/ year per patient on asthma-related healthcare.<sup>9</sup> In fact, severe asthma accounts for over 50% of the costs attributed to asthma of all severities.<sup>2</sup> Severe asthma is also clinically challenging to manage due to the extensive diagnostic and therapeutic interventions required for control and the need for personalised treatments.

To facilitate research and address the clinical challenges associated with managing severe asthma, several countries around the world such as Australia and New Zealand (Australasia),<sup>10</sup> Germany,<sup>11</sup> Italy,<sup>12–16</sup> Netherlands, South Korea,<sup>17</sup> Spain, United Kingdom,<sup>18–20</sup> and the United States began to establish national or local severe asthma registries. In response to calls from both the World Health Organization<sup>21</sup> and the Global Asthma Report<sup>22</sup> for better surveillance of chronic respiratory diseases including severe asthma, the International Severe Asthma Registry (ISAR; <http://isaregistries.org/>) was established in 2017.<sup>23,24</sup> ISAR is a global initiative and the largest adult severe asthma registry, currently including prospective data on 13,169 patients from 26 countries (as of October 2022). It was founded in partnership with national and regional severe asthma registries to act as a data custodian, storing standardised severe asthma data that can be shared for clinical and research purposes.<sup>23,25,26</sup> At the outset of ISAR, variables that pre-existing registries report collecting were studied and compared; the observed variations in data quality and definitions of severe asthma globally highlighted the need for standardisation. The set of core variables to be collected by severe asthma registries, including those planning to contribute to ISAR was identified using a modified Delphi method (Table 1).<sup>25</sup>

Once the core variables were standardised and collected by countries, ISAR-affiliated registries next started to collect optional steroid-related comorbidities and safety variables. Steroid-related comorbidity variables were collected in recognition of the increasing impact of systemic steroids in severe asthma and potential benefit of biologics in reducing steroid burden (Table 2). The safety variables are serious infections (eg, tuberculosis, pneumonia, meningitis, sepsis urinary tract infections), anaphylaxis, and cancer; these adverse events have been possibly associated with biologic initiation. Anti-immunoglobulin E (anti-IgE) and anti-interleukin 5/5 receptor (anti-IL-5/5R) therapies have been reported to show associations with anaphylaxis, indicating the need to monitor patients after administration of biologic treatment.<sup>27</sup> Biologic therapy may also impair the body's immune system and ability to respond to antigens, leading to increased risk of parasitic, bacterial, and viral infections.<sup>28,29</sup> Additionally, as eosinophils are involved in immune responses against certain cancers, and as anti-interleukin (IL)-5/5R and anti-IL-4/13 treatments inhibit eosinophil maturation and

activity, there is value in tracking the potential long-term cancer risk of biologic treatment in severe asthma.<sup>28</sup>

**Table 1** List of ISAR's Core and Optional Variables

Category	ISAR Variable
Core variables (ISAR-led Delphi study) <sup>3</sup>	
Inclusion criteria	Receiving GINA step 5 therapy Uncontrolled receiving GINA step 4 therapy
Demographics	Date of visit <sup>†</sup> Date of birth Age Gender Body mass index <sup>†</sup> Body surface area <sup>†</sup> Height <sup>†</sup> Weight <sup>†</sup> Ethnicity/Race
Occupation	Current occupation <sup>†</sup>
Medical history	Age of asthma onset Other asthma factors/types/triggers <ul style="list-style-type: none"> <li>• Exercise, occupation, menstruation, drugs, infections, irritants, weather, emotional, smoke, food, specific allergens, non-allergic, air pressure, cold, COPD overlap</li> </ul> Smoking status <sup>†</sup> Pack years <sup>†</sup> Years since the patient stopped smoking <sup>†</sup>
Medical history: Procedures	Bronchial thermoplasty <sup>†</sup>
Hospital resource use	Hospital visits <sup>†</sup> Emergency department visits <sup>†</sup> Asthma exacerbations <sup>†</sup> <ul style="list-style-type: none"> <li>• Exacerbation date*</li> <li>• Rescue steroid used: dose and frequency*</li> </ul> Invasive ventilation <sup>†</sup>
Comorbidities	Eczema Allergic rhinitis <sup>†</sup> Chronic rhinosinusitis <sup>†</sup> Nasal polyps <sup>†</sup> Atopic disease <sup>†</sup>
Diagnostic tests	Chest CT scan <sup>†</sup> Bone densitometry (DEXA) scan <sup>†</sup>
Laboratory tests	Highest blood eosinophil count details <sup>†</sup> Highest blood eosinophil count not during an exacerbation details <sup>†</sup> Current blood eosinophil count details Blood IgE count Sputum eosinophil count <sup>†</sup> Allergen test <sup>†</sup> <ul style="list-style-type: none"> <li>• Serum allergen test<sup>†</sup>Skin prick test<sup>†</sup></li> </ul> FeNO test <sup>†</sup>
Lung function	Bronchial provocation test <sup>†</sup> <ul style="list-style-type: none"> <li>• Adenosine monophosphate, exercise, histamine, hypertonic saline, mannitol, methacholine, prednisolone</li> </ul> Pre-bronchodilator FEV <sub>1</sub> <sup>†</sup> Pre-bronchodilator FVC <sup>†</sup> Post-bronchodilator FEV <sub>1</sub> <sup>†</sup> Post-bronchodilator FVC <sup>†</sup> Pre- and post-bronchodilator: Percentage of predicted FEV <sub>1</sub> and FVC <sup>†</sup> Pre- and post-bronchodilator: FEV <sub>1</sub> /FVC ratio <sup>†</sup>
Asthma control	GINA Asthma Control Questionnaire <sup>†</sup>

Category	ISAR Variable
Core variables (ISAR-led Delphi study) <sup>a</sup>	
Asthma medications	<p>OCS<sup>†</sup></p> <ul style="list-style-type: none"> <li>• OCS dose*</li> </ul> <p>ICS (only)<sup>†</sup></p> <ul style="list-style-type: none"> <li>• ICS dose*</li> </ul> <p>ICS + LABA combination therapy<sup>†</sup></p> <ul style="list-style-type: none"> <li>• ICS + LABA dose*</li> </ul> <p>LABA (only)<sup>†</sup></p> <p>LAMA<sup>†</sup></p> <p>Theophyllines<sup>†</sup></p> <p>Leukotriene receptor antagonist (LTRA)<sup>†</sup></p> <p>Anti-IgE treatment<sup>†</sup></p> <p>Anti-IL5 treatment<sup>†</sup></p> <p>Anti-IL4 treatment<sup>†</sup></p> <p>Macrolide antibiotic treatment<sup>†</sup></p> <p>Steroid sparing agents<sup>†</sup></p>
Treatment adherence and clinical management	<p>Adherence to treatment<sup>†</sup></p> <p>Current management plan<sup>†</sup></p> <p>Reason for medication switch between biologics/OCS*</p> <ul style="list-style-type: none"> <li>• Lack of efficacy, side-effects, drug access influences/restrictions, patient preferences, federal/regional/national/hospital drug provision, compassionate program for drugs, insurance coverage</li> </ul>
Optional steroid-related comorbidity variables (as established by ISAR) <sup>b</sup>	
Steroid-related comorbidities*	<p>Obstructive sleep apnoea<sup>†</sup></p> <p>Depression<sup>†</sup></p> <p>Anxiety<sup>†</sup></p> <p>Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism)<sup>†</sup></p> <p>Osteoporosis<sup>†</sup></p> <p>Type 2 diabetes<sup>†</sup></p> <p>Pneumonia<sup>†</sup></p> <p>Ocular diseases (Cataract, glaucoma)<sup>†</sup></p> <p>Chronic Kidney Disease (report collecting under the variable name "Renal Failure" in ISAR)<sup>†</sup></p> <p>Peptic ulcer<sup>†</sup></p>
Optional safety variables (as established by ISAR) <sup>b</sup>	
Safety of biologics	<p>Serious infection<sup>†</sup></p> <p>Anaphylaxis<sup>†</sup></p> <p>Cancer<sup>†</sup></p>
COVID-19 variables (as established by ISAR)	
Confirmation of COVID-19 infection	<p>Positive laboratory test<sup>†</sup></p> <p>Clinical presentation and radiology<sup>†</sup></p>
COVID-19 diagnostic test	<p>PCR<sup>†</sup></p> <p>Antigen panel<sup>†</sup></p> <p>Antibody panel<sup>†</sup></p> <p>Chest X-ray<sup>†</sup></p> <p>Chest CT scan<sup>†</sup></p>
COVID-19 diagnostic test date <sup>†</sup>	
Biomarker test during COVID-19 infection	<p>Lactate dehydrogenase (LDH)<sup>†</sup></p> <p>D-dimer<sup>†</sup></p> <p>Ferritin<sup>†</sup></p> <p>C-Reactive Protein (CRP)<sup>†</sup></p> <p>Procalcitonin<sup>†</sup></p>



Category	ISAR Variable
Core variables (ISAR-led Delphi study) <sup>3</sup>	
COVID-19 diagnostic test	PCR <sup>†</sup> Antigen panel <sup>†</sup> Antibody panel <sup>†</sup> Chest X-ray <sup>†</sup> Chest CT scan <sup>†</sup>
COVID-19 diagnostic test date <sup>†</sup>	
Biomarker test during COVID-19 infection	Lactate dehydrogenase (LDH) <sup>†</sup> D-dimer <sup>†</sup> Ferritin <sup>†</sup> C-Reactive Protein (CRP) <sup>†</sup> Procalcitonin <sup>†</sup>
Biomarker test result <sup>†</sup>	
Biomarker test date <sup>†</sup>	
Respiratory symptoms during COVID-19 infection	Cough Wheezing Chest tightness Runny nose Nasal congestion Sputum/phlegm production Shortness of breath/difficulty breathing Daytime symptoms Nocturnal symptoms Reliever medication use Activity limitation
Change in respiratory symptoms during COVID-19 infection period <sup>†</sup>	
Events during COVID-19 infection	Exacerbation <sup>†</sup> Hospitalization <sup>†</sup> Emergency department visit <sup>†</sup> Invasive ventilation (endotracheal intubation) <sup>†</sup> Non-invasive ventilation (CPAP, BiPAP) <sup>†</sup> Receipt of high-flow oxygen <sup>†</sup> Disruption/ changes to usual asthma care <sup>†</sup> Death <sup>†</sup>
Event date <sup>†</sup>	
Treatment for COVID-19 infection <sup>†</sup>	
Treatment name <sup>†</sup>	
Treatment start/ end dates or prescription duration <sup>†</sup>	

Notes: <sup>3</sup>ISAR core variables beyond those derived from the Delphi study,<sup>4</sup> which provide information on OCS use.<sup>5</sup>ISAR variables registries report collecting at baseline visits and follow-up visits.<sup>6</sup>Bulathsinhala L, et al. *J Allergy Clin Immunol Pract* 2019;7(2):578–588.e2.<sup>7</sup>FitzGerald JM, et al. *BMC Med. Res. Methodol* 2020; 20:212. The following 5 variables “exacerbation date, rescue steroid used (including dose and frequency), OCS dose and prescription dates, ICS dose and prescription dates, ICS+LABA dose and prescription dates” have been presented as core variables in the inventory manuscript (as per our CRF and data collection methods) but are considered effectiveness bolt-on variables in ISAR for contractual purposes. These 5 variables are not part of the core variable list from the Delphi study (Bulathsinhala L, et al. *J Allergy Clin Immunol Pract*. 2019;7(2):578–588.e2).

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; DEXA, dual energy X-ray absorptiometry; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL4, interleukin 4; IL5, interleukin 5; ISAR, International Severe Asthma Registry; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroids.

**Table 2** List of Identified Severe Asthma Registries Worldwide

Country	Name	Start Year	Number of Centres	Number of Patients	Date of Estimation
ISAR-affiliated severe asthma registries					
Argentina	Argentinian Severe Asthma Registry	2019	19	126	11/11/21
Australia and New Zealand	Australasian Severe Asthma Network Registry (ASAN), previously Severe Asthma Web-based Database (SAWD) <sup>10</sup>	2019	23	400	09/11/21
Belgium	University of Liege	2023	1	744	19/06/2023
Bulgaria	Bulgarian Severe Asthma Registry	2019	11	325	08/07/22
Canada	Canadian Severe Asthma Registry	2018	10	253	30/06/22
Colombia	Colombian Severe Asthma Registry	2019	3	291	29/06/22
Denmark	Danish Severe Asthma Registry (DSAR) <sup>30</sup>	2018	9	567	08/07/22
Estonia	Estonian Severe Asthma Registry	TBC	1	TBC	18/12/20
Greece	Greek Severe Asthma Registry	2016	4	151	08/07/22
India	Pulmocare Research and Education (PURE) Foundation	2020	37	155	11/11/21
Ireland	Irish Severe Asthma Registry	2020	1	42	07/07/22
Italy	Severe Asthma Network in Italy (SANI) <sup>12-16</sup>	2016	55	1600	08/11/21
Japan	Kinki-Hokuriku Airway disease Conference (KiHAC) <sup>31-33</sup>	2019	17	185	10/07/22
Kuwait	Kuwaiti Severe Asthma Registry	2018	1	284	08/07/22
Mexico	Mexican Severe Asthma Registry	2019	12	71	23/07/22
Poland	Polish Severe Asthma Registry	2021	1	29	11/11/21
Portugal	Portugal Severe Asthma Registry <sup>34</sup>	2018	18	132	07/07/22
Saudi Arabia	Saudi Arabian Severe Asthma Registry	2019	5	207	11/11/21
Singapore	Singapore Severe Asthma Registry (S-SAR)	2020	4	160	29/06/22
South Korea	Korean Severe Asthma Registry (KoSAR) <sup>17</sup>	2018	1	163	29/06/22
Spain	Spanish Guideline on the Management of Asthma Database (GEMA-Data)	2017	50	715	12/10/21
Sweden	Swedish Severe Asthma Registry – under development	TBC	1	TBC	Unknown
Taiwan	Taiwanese Severe Asthma Registry	2019	14	276	11/11/21
United Arab Emirates	United Arab Emirates Severe Asthma Registry	2019	1	229	29/06/22
United Kingdom	UK Severe Asthma Network and National Registry, previously British Thoracic Society Severe Asthma Registry <sup>18-20</sup>	2015	39	6225	08/07/22
United States	National Jewish Health (NJH)	2008 / 2017	1	5230	08/07/22

Country	Name	Start Year	Number of Centres	Number of Patients	Date of Estimation
Non-ISAR-affiliated registries					
Belgium	Belgian Respiratory Society <sup>35-37</sup>	2018	28	1653	30/06/22
Brazil	Brazilian Severe Asthma Group (BraSA Group)	TBC	16	TBC	14/04/21
Finland	Finnish Asthma Registry (Finland)	2020	3	200	01/07/22
France	Recherche sur les Asthmes Sévères (RAMSES)	2019	47	1050	25/10/21
Germany	German Severe Asthma Network (GAN) <sup>11</sup>	2011	30	1200	12/11/21
Germany	University Medical Center Essen-Ruhrlandklinik	2020	1	100	Unknown
Hungary	Hungarian Severe Asthma Registry	TBC	Unknown	Unknown	Unknown
Iceland	Asthmabio	2020	Unknown	206	07/07/22
Netherlands	Registry of Adult Patients with Severe Asthma for Optimal Disease Management (RAPSODI)	2016	20	933	14/06/21
Norway	Norwegian Severe Asthma Registry	2022	1	Zero - Patients to be enrolled	05/08/22
United States	CHRONICLE <sup>38</sup>	2018	127	3370	01/07/22

Severe asthma registries are collecting COVID-19 variables (eg, biomarker tests, respiratory symptoms, asthma outcomes, and COVID-19-related healthcare resource utilisation) as a result of the associated pandemic (Table 1). Although higher frequencies of COVID-19 in patients with asthma have not been identified,<sup>39</sup> severe COVID-19 in patients with severe asthma is possible.<sup>40</sup> Reports suggest hospitalised patients with severe asthma and COVID-19 infection have poorer outcomes, and biologics for severe asthma did not significantly impact COVID-19 outcomes.<sup>40</sup>

Many individual registries also reported collecting additional variables outside the scope of ISAR's core and optional categories in accordance with their individual research interests. This shows the diversity and complexity of the management of patients with severe asthma globally.

Establishing standardised variables and classifying them according to appropriate themes provides greater consistency and depth of data on patients with severe asthma globally. Likewise, encouraging individual registries to collect additional variables increases the breadth of data being collected. Currently, the inter-registry variability in data being collected is unknown. Our paper aims to describe the current global severe asthma registry landscape by summarising the variables collected by each registry and how they align with those of ISAR, as well as the variables that are collected in addition. It is anticipated that surveying the consistency, depth, and breadth of variables collected by severe asthma registries worldwide will highlight the existing resources for managing and studying severe asthma.

# Methods

## Identification of Registries

Severe asthma registries contributing data to the ISAR initiative (ISAR-affiliated) and those collecting data independent of ISAR (non-ISAR-affiliated) were included in the present analysis. Individual local (those of local sites or hospitals), national (those of countries), and regional registries (the regional registry included in this study is that of Australia and New Zealand [Australasia]) were identified by a systematic online search (up to August 2022), and by approaching 36 severe asthma experts globally to identify active, though not yet published registries. PubMed, MEDLINE, EMBASE, Google Scholar, and Web of Science databases were queried using the following keywords and combinations thereof: “severe asthma”, “difficult asthma”, “therapy-resistant asthma”, “severe refractory asthma”, “uncontrolled asthma”, “registry”, “repository”, “database”, “clinical trial records” and “clinical health records”. Registries that qualified for inclusion were those that collected data on adult patients with asthma and required patients to have a confirmed diagnosis of severe asthma. A confirmed diagnosis of severe asthma was defined as receiving GINA 2018 step 5 therapy, or uncontrolled asthma receiving GINA 2018 step 4 therapy (Table 1).<sup>41</sup> Registries that either collected data on children only, contained information only on specific asthma drugs, were general asthma registries, or were non-contactable were excluded. No registries that were invited refused participation.

## Identification and Categorisation of Variables

Eligible registries opting to participate in the present study provided a list of variables they reported collecting in their case report forms or data collection specifications. In this manuscript, “reported” indicates past, current and/or planned data collection. Individual variables were then identified and assigned into one of three main categories: core variables (those identified in the ISAR-led Delphi study),<sup>25</sup> steroid-related comorbidities / safety variables (“optional” as established by ISAR), and additional variables (any other variable collected by a registry, which does not meet the criteria for inclusion into the core or optional categories) (Table 1). In line with current events, some countries also reported collecting COVID-19 variables to determine COVID-19’s potential association with severe asthma (Table 1).

## Assessment of Variables That Participating Registries Reported Collecting

Once categorised, the proportion of core variables that each registry reported collection of was calculated. The steroid- related comorbidities / safety variables, additional variables and COVID-19 variables that registries reported collecting were also summarised. In this manuscript, counts and percentages are presented to summarise data in tables and the Figure. In due course, ISAR will use any suitable statistics to analyse and report observational data according to STROBE guidance.<sup>42</sup> Similarly, to conduct and report prediction models, whether for diagnostic or prognostic purposes, we will endorse TRIPOD guidance.<sup>43</sup>

# Results

## Identification of Registries

Thirty-seven individual registries from 35 different countries were identified. All 37 registries opted to participate in this study. Of the identified registries, 26 were ISAR affiliates and the remaining 11 were independent at the time of publication (Table 2). ISAR-affiliated registries were from Argentina, Australia and New Zealand (Australasia), Belgium, Bulgaria, Canada, Colombia, Denmark, Estonia, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Taiwan, United Arab Emirates, the United Kingdom, and the United States (National Jewish Health). Non-ISAR-affiliated registries as of September 2022 were from Belgium, Brazil, Finland, France, Germany (2 registries), Hungary, Iceland, Netherlands, Norway, and the United States (CHRONICLE). Characteristics of these registries, such as the numbers of centres and patients in each registry, have been outlined in Table 2.

## Assessment of Core Variables That Registries Reported Collecting

Sixty-five Delphi-derived core variables were analysed<sup>25</sup> (Table 1 and Supplementary Tables 1.1 and 1.2). The 95 variables in the ISAR Delphi publication were categorized and represented as 65 core variables in the tick table of this study. For example, the serum allergy test “positivity”, “result” and “date” were 3 separate variables in the ISAR Delphi publication, but were categorized as 1 core variable “serum allergy test” in the tick table of this study. The following 5 variables “exacerbation date, rescue steroid used (including dose and frequency), OCS dose and prescription dates, ICS dose and prescription dates, ICS+LABA dose and prescription dates” have been presented as core variables in the inventory manuscript (as per our CRF and data collection methods) but are considered effectiveness bolt-on variables in ISAR for contractual purposes.<sup>25</sup> These 5 variables are not part of the core variable list from the Delphi study. Twenty-five ISAR-affiliated registries reported collection of all core variables (Figure 1). Five non-ISAR-affiliated registries reported collection of >90% of core variables, with the Brazil Severe Asthma Group (BraSA) and the United States (CHRONICLE) reporting collection of all core variables. Core variables that non-ISAR-affiliated registries were less likely to report collecting compared to ISAR-affiliated registries include rescue steroid (ie, OCS) information (55% [n = 6/11] of non-ISAR-affiliated registries, 92% [n = 24/26] of ISAR-affiliated registries), details of highest blood eosinophil count (BEC) not during an exacerbation (55% [n = 6/11] of non-ISAR-affiliated registries, 92% [n = 24/26] of ISAR-affiliated registries), exacerbation date (27% [n = 3/11] of non-ISAR-affiliated registries, 92% [n = 24/26] of ISAR-affiliated registries), bronchial provocation test (64% [n = 7/11] of non-ISAR-affiliated registries, 100% of ISAR-affiliated registries).

## Assessment of Steroid-Related Comorbidities / Safety Variables That Registries Reported Collecting

Twenty-three of the 37 registries (19 ISAR-affiliated and 4 non-ISAR-affiliated) reported collecting all optional steroid related comorbidity variables. 78% of registries (n = 29/37; 23 ISAR-affiliated and 6 non-ISAR-affiliated) reported collecting all optional safety variables (Table 3).

**Table 3** Summary of ISAR Optional Variables and Key Non-ISAR Additional Variables That Severe Asthma Registries Worldwide Report Collecting

Country	ISAR Optional Steroid-Related Comorbidity Variable <sup>a</sup>	ISAR Optional Safety Variables <sup>b</sup>	Key Non-ISAR Additional Variables
ISAR-affiliated severe asthma registries			
Argentina	All	All	ACT
Australia and New Zealand	Obstructive sleep apnoea Depression Anxiety Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Osteoporosis Type 2 diabetes	Anaphylaxis	Peak expiratory flow ACT, ACQ and AQLQ SABA use
Belgium	Nil	Nil	ACT, ACQ and AQLQ SABA and LABA + LAMA use
Bulgaria	All	All	Passive smoking and family history of asthma Sputum culture and sputum IgE Peak expiratory flow ACT, ACQ, AQLQ and EQ-5D-5L SABA and LABA + LAMA use Database linkage with outpatient and inpatient databases
Canada	All	All	ACT, ACQ, AQLQ and EQ-5D-5L
Colombia	All	All	–
Denmark	Obstructive sleep apnoea Depression Anxiety Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Osteoporosis Type 2 diabetes Pneumonia	All	ACQ SABA and LABA + LAMA use Database linkage with: <ul style="list-style-type: none"> <li>• Danish National Prescription Registry<sup>44</sup></li> <li>• Danish National Patient Registry<sup>45</sup></li> <li>• Civil Registration System<sup>46</sup></li> <li>• Danish Cancer Registry<sup>47</sup></li> <li>• Danish Psychiatric Central Research Register<sup>48</sup></li> <li>• Danish Register of Causes of Death<sup>49</sup></li> <li>• Income Statistics Register<sup>50</sup></li> <li>• Clinical Laboratory Information System<sup>51</sup></li> <li>• Danish Education Registers<sup>52</sup></li> </ul>
Greece	All	All	Family history of asthma ICU admissions ACT SABA and LABA + LAMA use
India	All	All	–
Ireland	All	All	Family history of asthma Peak expiratory flow ACT, AQLQ and EQ-5D-5L SABA and LABA + LAMA use
Italy	All except Depression	All	Non-invasive ventilation and ICU admissions ACT, ACQ and AQLQ SABA use
Japan	All	All	Passive smoking ACT and JACS
Kuwait	All	All	–

Country	ISAR Optional Steroid-Related Comorbidity Variable <sup>1</sup>	ISAR Optional Safety Variables <sup>2</sup>	Key Non-ISAR Additional Variables
Mexico	All	All	Mini-AQLQ Allergen immunotherapy (AIT)
Poland	All	All	–
Portugal	All	All	Passive smoking and family history of asthma Non-invasive ventilation and ICU admissions Peak expiratory flow ACT, ACQ and AQLQ SABA use
Saudi Arabia	All	All	–
Singapore	All	All	ACT and ACQ
South Korea	All except Anxiety	None	Family history of asthma Peak expiratory flow ACT and AQLQ SABA and LABA + LAMA use
Spain	Obstructive sleep apnoea Depression Anxiety Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Osteoporosis	All	Family history of asthma ACT SABA use
Sweden	Obstructive sleep apnoea Depression Anxiety Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Type 2 diabetes Pneumonia Ocular diseases (Cataract, glaucoma)	All	Database linkage
Taiwan	All	All	ACT Database linkage
United Arab Emirates	All	All	–
United Kingdom	All	All	Non-invasive ventilation and ICU admissions ACQ and EQ-5D-5L SABA and LABA + LAMA use
United States (National Jewish Health)	All	All	Passive smoking and family history of asthma ICU admissions Sputum culture and sputum IgE ACT, ACQ and AQLQ SABA and LABA + LAMA use Database linkage with EMR
Non-ISAR-affiliated severe asthma registries			
Belgium	Obstructive sleep apnoea Depression Anxiety Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Pneumonia Peptic ulcer	Serious infection Anaphylaxis	Family history of asthma Loss of asthma control when stepping down from high ICS doses SABA use

Country	ISAR Optional Steroid-Related Comorbidity Variable <sup>9</sup>	ISAR Optional Safety Variables <sup>1</sup>	Key Non-ISAR Additional Variables
Brazil	All	All	–
Finland	All	All	ACT Database linkage with hospital medical records (connected with the national prescription database) and patient applications database
France	All	All	Family history of asthma ICU admissions ACT, AQLQ and EQ-5D-5L, SGRQ SNOT-22 LABA + LAMA use Database linkage with the National Health Insurance Database (SNDS)
Germany (University Medical Center Essen-Ruhrlandklinik)	Obstructive sleep apnoea	None	–
Germany (German Asthma Network)	Depression Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Pneumonia	Serious infection	Passive smoking Peak expiratory flow ACT, ACQ and AQLQ SABA and LABA + LAMA use
Hungary	All except Chronic kidney disease	All	Passive smoking Family history of asthma ICU admissions Peak Expiratory Flow ACT, ACQ, EQ-5D-5L, SABA SAMA SABA + SAMA LABA + LAMA use
Iceland	Obstructive sleep apnoea Depression Anxiety Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Type 2 diabetes Pneumonia Ocular diseases (Cataract, glaucoma)	All	Database linkage
Netherlands	Obstructive sleep apnoea Depression Anxiety Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Type 2 diabetes Pneumonia Ocular diseases (Cataract, glaucoma)	Serious infection	Sputum culture SABA and LABA + LAMA use
Norway	Obstructive sleep apnoea Depression Anxiety Circulatory system disease (Heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism) Type 2 diabetes Pneumonia Ocular diseases (Cataract, glaucoma)	All	ACT SABA SAMA SABA + SAMA LABA + LAMA use
United States (CHRONICLE)	All	All	ACT/AIRQ, SGRQ, WPAI-Asthma GETE Passive smoking and family history of asthma Non-invasive ventilation and ICU admissions Sputum culture Peak expiratory flow SABA and LABA + LAMA use

**Notes:** <sup>9</sup>Full list of ISAR optional safety comorbidity variables: Obstructive sleep apnoea, depression, anxiety, circulatory system disease (heart failure, myocardial infarction, pulmonary embolism/venous thromboembolism), osteoporosis, type 2 diabetes, pneumonia, ocular diseases (cataract, glaucoma), chronic kidney disease and peptic ulcer; <sup>1</sup>Full list of ISAR optional safety variables: Serious infection, anaphylaxis and cancer. The following 5 variables "exacerbation date, rescue steroid used (including dose and frequency), OCS dose and prescription dates, ICS dose and prescription dates, ICS+LABA dose and prescription dates" have been presented as core variables in the inventory manuscript (as per our CRF and data collection methods) but are considered effectiveness bolt-on variables in ISAR for contractual purposes. These 5 variables are not part of the core variable list from the Delphi study (Bulathsinhala L. et al. *J Allergy Clin Immunol Pract.* 2019;7(2):578–588).  
**Abbreviations:** ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; EMR, electronic medical record; EQ-5D-5L, EuroQoL 5-dimension 5-level Questionnaire; ICS, inhaled corticosteroids; ICU, intensive care unit; IgE, immunoglobulin E; JACS, Japan Asthma Control Survey; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; SABA, short-acting beta-agonists.



## **Assessment of Additional Variables That Registries Reported Collecting**

Key additional non-ISAR variables that registries reported collecting include information on family history of asthma, intensive care unit admissions, use of acute non-invasive ventilation, sputum culture, peak expiratory flow, patient reported outcome measures (such as Asthma Control Test [ACT],<sup>53</sup> Asthma Control Questionnaire [ACQ],<sup>54</sup> Asthma Quality of Life Questionnaire [AQLQ],<sup>55</sup> and EuroQol 5-dimension 5-level Questionnaire [EQ-5D-5L]),<sup>56</sup> and database linkage (Table 3). In particular, 25 registries (18 ISAR affiliated and seven non-ISAR-affiliated) reported collecting data from patient-reported outcome measures (12 report collecting ACQ, 22 report collecting ACT, 12 report collecting AQLQ,<sup>55</sup> and 4 report collecting EQ-5D-5L). Eight registries (five ISAR affiliated and three non-ISAR-affiliated) are linked or plan to be linked to databases such as hospital or clinic electronic medical records (EMRs), prescription databases, national disease databases, or national insurance databases (Table 3).

## **Assessment of COVID-19 Variables That Registries Reported Collecting**

Since the beginning of the COVID-19 pandemic, ten registries (seven ISAR-affiliated and three non-ISAR-affiliated) reported collection of COVID-19 variables to determine COVID-19's potential association with severe asthma outcomes. Variables that countries reported collecting include confirmation of COVID-19 infection, COVID-19 diagnostic tests, biomarker tests and results, respiratory symptoms, and changes in respiratory symptoms (if any) during a COVID-19 infection. All ISAR-affiliated registries also reported collecting data on key events such as exacerbations, hospitalisations, and emergency department visits during a COVID-19 infection, as well as data on COVID-19 treatments.

## **Discussion**

The majority of severe asthma registries, regardless of ISAR affiliation, reported collection of >90% of ISAR's core variables (Table 1). Most, if not all registries reported collecting safety variables and OCS comorbidity data (Table 3 and Supplementary Tables 1.1 and 1.2), reflecting a common goal of documenting OCS burden and safety events in patients. The registries' use of patient-reported outcome measures demonstrates a shared goal of monitoring and quantifying patient outcomes, whereas the reported collection of COVID-19 variables reflects an aim of optimising severe asthma care and research. The collation of variables in a single tick table (Supplementary Tables 1.1 and 1.2) helps promote collaboration and communication across registries and the wider severe asthma community. Additionally, the practice of database linkage by Bulgaria, Denmark, Finland, France, Iceland, Sweden, Taiwan, and the United States (NJH) is beneficial as the access to data from EMRs and national databases (national claim databases, national prescription databases, etc) can improve the robustness of research involving people who have severe asthma (Table 3).

ISAR is the first global, collaborative effort to standardise and consolidate data collection across national and regional registries. The ability to collect a standardised set of variables while maintaining individuality enables registries to develop locally relevant research priorities and clinical interests.<sup>23</sup> The extent of data collected also allows for ISAR to adapt to variations in definitions of disease and treatments, and consequently, flexibility in research. Further, ISAR's data interoperability allows for pooling of data across 26 countries, contributing prospectively collected data for 13,169 patients (as of October 2022). Thus,

ISAR is able to answer important research questions on severe asthma with sufficient statistical power.<sup>24</sup> The collation of data into ISAR's centralised repertoire enables the ENLIGHTEN research program with projects on the characterisation and care of patients with severe asthma, and the effectiveness of biologic therapy.<sup>57</sup> ISAR's first global publication describes the demographic and clinical features of patients with severe asthma, including variations in exacerbation rates and healthcare resource utilisation.<sup>3</sup> Documenting such international variations can indicate gaps in care or differences in exposures and risk factors for asthma. Similarly, five distinct patient clusters with unique clinical characteristics were identified through biomarker expression in the BRISAR project, providing insights into the delivery of personalised medicine.<sup>58</sup>

ISAR creates opportunities to identify and improve the clinical management of patients with severe asthma. For example, the ISAR eosinophil gradient algorithm, which was built using ISAR data and expert consensus, identified 83.8% of patients to be likely eosinophilic (grade 3).<sup>59</sup> However, there is possible bias towards eosinophilic phenotypes as some ISAR registries only recruit patients who are prescribed biologic therapies. ISAR's research has also brought awareness to the effectiveness of biologics. For example, although both anti-IgE and anti-IL-5/5R therapies reduced exacerbations rates and long-term OCS daily dose in the FIRE study, anti-IL-5/5R therapy appeared to be more effective.<sup>60</sup> The BEAM study will inform future work on response and predictors of response.<sup>61,62</sup> Additionally, patients prescribed biologic therapies showed greater improvements in severe asthma outcomes than patients who continued high OCS exposure (HOCS) in the GLITTER study.<sup>63,64</sup> These findings may influence guidelines to recommend biologics, even in patients showing improvement on OCS. The global variations in access to biologics illustrated by the BACS study should also be acknowledged.<sup>65</sup> The PRISM study showed that comorbidities were associated with increased exacerbation rates in patients with severe asthma.<sup>66</sup> Further research on the impact of biologics in patients with severe asthma and comorbidities is needed to inform the development of clinical guidelines.

Research from individual registries has also expanded the current understanding of severe asthma. Several population-based registries, including the Korean Severe Asthma Registry (KoSAR), the German Asthma Network (GAN) and the UK Severe Asthma Registry (UKSAR) have described the prevalence and characteristics of severe asthma in their respective countries.<sup>11,17,18</sup> National registry data from countries including Belgium, Italy, and the UK have been used to quantify biologic use, exacerbations, BEC, OCS exposure, comorbidity prevalence, and investigate associations between biologics and asthma outcomes (eg, exacerbations and lung function decline).<sup>12,18,19,35</sup>

ISAR's collaboration with other severe asthma registries has also influenced the development of current research agendas. The SUNNIE study used data from ISAR and CHRONICLE (USA) to describe biologic utilisation worldwide.<sup>67</sup> CHRONICLE is a real-world, prospective, non-interventional cohort study of US specialist-treated patients with severe asthma.<sup>38</sup> The SUNNIE study identified that three-quarters of patients remain on their first biologic treatment and the most common switch is from anti-IgE to anti-IL-5/5R therapy.<sup>67</sup>

The key strength of the current study is that the named registries were collaborators, and freely shared their data collection specifications. Furthermore, the inventory of variables provided by this study could be a starting point for new severe asthma registries while enabling existing registries to identify potential gaps in their data collection. An additional

strength of ISAR is flexibility to adapt to new variations in asthma definitions and treatments, such as treatable traits and the asthma-COPD overlap,<sup>68</sup> and else.

The main limitation of this study is the difficulty in ascertaining the actual collection of variables (ie, the extent of missing data and whether they were systematic or random) and should be a feature of future research. Secondly, it is possible local severe asthma registries were not identified by the online search or severe asthma experts. Thirdly, the interpretation of data field names may differ slightly across countries, potentially affecting the study's findings. Finally, the current study only analysed local, national or regional severe asthma registries; analyses of continental registries such as the pan-European Severe Heterogeneous Asthma Research Collaboration, Patient-centred (SHARP),<sup>69</sup> were not included as per the ISAR protocol. Even though SHARP's four primary aims "1) end dependency on systemic corticosteroids for asthma control, 2) enable access to severe asthma specialists for all people with severe asthma, 3) improve understanding of the heterogeneity of severe asthma mechanisms, and 4) seek to prevent the development of severe forms of asthma<sup>69</sup> overlaps with ISAR's vision for the future, analyses of continental registries were beyond the current study's scope.

As a growing inventory, ISAR looks to welcome additional registries from the US that are based at the University of North Carolina and the University of Texas, San Antonio as well as registries from Malaysia and Ecuador in the near future. Meanwhile, to ensure future sustainability, severe asthma registries should continue to evolve through quality improvement initiatives. For example, ISAR's interactive asthma reports that will be used by registries and patients will track the status of patients over time, enhancing their care. The ISAR tools are flexible and interactive, with a potential to produce asthma reports at the individual patient level or pooled by site, or by country for international comparisons. Individual countries have also employed quality improvement initiatives. In Canada, an algorithm to identify severe asthma in primary care EMRs based on Pan-Canadian Respiratory Standards Initiative for Electronic Health Record (PRESTINE) and core asthma elements were developed by experts using a modified Delphi process.<sup>70,71</sup> Subsequently, PRESTINE developed severe asthma elements for specialists' EMRs, and an algorithm to identify severe asthma using the core elements in primary care EMRs.<sup>70,71</sup> In Denmark, the data collection platform for its severe asthma registry is a research database and medical record form.<sup>30</sup> The Portuguese registry is linked to a mobile app that collects self-reported data (eg, sociodemographics, history of asthma, exacerbations, comorbidities, etc.) that are verified and validated by a physician before being saved to the registry's database. Such knowledge translation and quality improvement initiatives also eliminate the need for dual data entry and enable evidence-based asthma management.

## **Conclusion**

The ISAR initiative has fostered data standardisation across countries, improving the external validity and accuracy of severe asthma research. Irrespective of registries' affiliations with ISAR, ISAR and individual registries complement each other. Allowing registries to retain ownership over their data enables an informed data collection process that serves local, regional, or national clinical needs and research interests. Importantly, knowledge gained from research outputs from severe asthma registries worldwide can inform local health policy, be incorporated into clinical guidelines, and be translated into quality improvement programs that enhance the care of asthma patients globally.

## **Ethics Statement**

Registration of the ISAR database with the European Union Electronic Register of Post-Authorization studies was also undertaken (ENCEPP/DSPP/23720). ISAR has ethical approval from the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218). All data collection sites in the International Severe Asthma Registry (ISAR) have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards and organizations.

The ethics application process differs among participating registries/countries in ISAR. Within some registries, ethics approval is required at each individual satellite site, whereas for other collaborators, a central ethics committee can process applications on behalf of all satellite sites. Informed consent was obtained from patients where required to allow anonymised data sharing for approved research projects in ISAR.

The guidelines outlined in the Declaration of Helsinki were followed.

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Optimum Patient Care and AstraZeneca. Celine Yun Yi Goh is an employee of Optimum Patient Care Global (OPCG), a co-funder of the International Severe Asthma Registry. Rebecca Vella is an employee of Optimum Patient Care, a co-funder of the International Severe Asthma Registry. Neva Eleangovan was an employee of the Observational and Pragmatic Research Institute (OPRI). OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca. Lakmini Bulathsinhala is an employee of the Observational and Pragmatic Research Institute (OPRI). OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca. Jorge F Maspero reports speaker fees, grants or advisory boards for AstraZeneca, Sanofi, GSK, Novartis, Immunotek, Menarini, Noucor. Matthew J Peters declares personal fees and non-financial support from AstraZeneca and GlaxoSmithKline. Florence Schleich reports consultancy work for GSK, AstraZeneca, Sanofi - Advisory board, received speaker fees from GSK, AstraZeneca, Chiesi, Amgen, TEVA and research grants from GSK, AstraZeneca, Chiesi. Paulo Pitrez received fees as speaker or for consultations from GSK, AstraZeneca, Novartis, Sanofi, and Boehringer Ingelheim. George Christoff declares no relevant conflicts of interest in this work. Mohsen Sadatsafavi has received honoraria from AZ, BI, TEVA, and GSK for purposes unrelated to the content of this manuscript and has received research funding from AZ and BI directly into his research account from AZ for unrelated projects. Carlos A. Torres-Duque has received fees as advisory board participant and/or speaker from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis and Sanofi-Aventis; has taken part in clinical trials from AstraZeneca, Novartis and Sanofi-Aventis; has received unrestricted grants for investigator-initiated studies at Fundacion Neumologica Colombiana from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Grifols and Novartis. Celeste Porsbjerg has attended advisory boards for AstraZeneca, Novartis, TEVA, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, TEVA, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, MSD, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research grants from AstraZeneca, Novartis, TEVA, GlaxoSmithKline, ALK, and Sanofi-Genzyme. Alan Altraja has received lecture fees from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; sponsorships from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, and Sanofi; and has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi, and Teva. Lauri Lehtimäki has received personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Menarini, Novartis, Orion Pharma and Sanofi. Arnaud Bourdin has received industry-sponsored grants from AstraZeneca-MedImmune, Boehringer-Ingelheim, Cephalon/Teva, GlaxoSmithKline, Novartis, Sanofi-Regeneron and consultancies with AstraZeneca-MedImmune, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Regeneron-Sanofi, Med-in-Cell, Actelion, Merck, Roche, and Chiesi. Christian Taube declares no relevant conflicts of interest in this work. Nikolaos G. Papadopoulos has been a speaker and/or advisory board member for Abbott, Abbvie, ALK, Asit Biotech, AstraZeneca, Biomay, Boehringer Ingelheim, GSK, HAL, Faes Farma, Medscape, Menarini, MSD, Mylan, Novartis, Nutricia, OM Pharma, Regeneron, Sanofi, Takeda, Viatrix. He also reports research support from Capricare, Nestle, Numil, Vianex, and REG, outside the submitted work. Zsuzsanna Csoma declares no relevant conflicts of interest in this work. Unnur Bjornsdottir receives gratuities for lectures/presentations from AstraZeneca, Sanofi and Novartis. Sundeep Salvi declares research support and speaker fees from Cipla, Glenmark, GSK. Enrico Heffler declares personal fees from: Sanofi, Regeneron, GSK, Novartis, Astrazeneca, Stallergenes, Circassia. Takashi Iwanaga received lecture fees from Kyorin, GlaxoSmithKline, Novartis, Boehringer Ingelheim and AstraZeneca. Mona Al-Ahmad has received advisory board and

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